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(54) Title: USE OF RAPAMYCIN AND RAPAMYCIN DERIVATIVES FOR THE TREATMENT OF BONE LOSS

(57) Abstract: The present invention relates to a new use of rapamycin and rapamycin derivatives.

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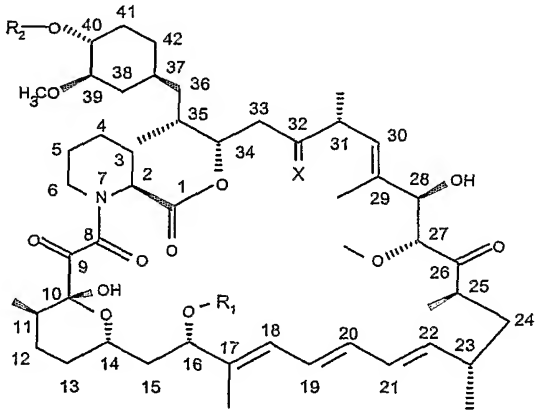
USE OF RAPAMYCIN AND RAPAMYCIN DERIVATIVES FOR THE TREATMENT OF BONE LOSS

The present invention relates to a new use of rapamycin and rapamycin derivatives.

Rapamycin is an immunosuppressive lactam macrolide that is produced by Streptomyces hygroscopicus.

A rapamycin derivative is a substituted rapamycin e.g. a 40-O-substituted rapamycin e.g. as described in US 5 258 389, WO 94/09010, WO 92/05179, US 5 118 677, US 5 118 678, US 5 100 883, US 5 151 413, US 5 120 842, WO 93/11130, WO 94/02136, WO 94/02485 and WO 95/14023 all of which are incorporated herein by reference; a 16-O-substituted rapamycin e.g. as disclosed in WO 94/02136, WO 95/16691 and WO 96/41807, the contents of which are incorporated herein by reference; or a 32-hydrogenated rapamycin e.g. as described in WO 96/41807 and US 5 256 790, incorporated herein by reference.

Preferred rapamycin derivatives are compounds of formula I



I

wherein

R_1 is CH_3 or C_{3-6}alkynyl,

R_2 is H or $-CH_2-CH_2-OH$, 3-hydroxy-2-(hydroxymethyl)-2-methyl-propanoyl or tetrazolyl, and X is =O, (H,H) or (H,OH)

provided that R_2 is other than H when X is =O and R_1 is CH_3,

or a prodrug thereof when R_2 is $-CH_2-CH_2-OH$, e.g. a physiologically hydrolysable ether thereof.

Particularly preferred rapamycin derivatives of formula I are 40-O-(2-hydroxyethyl)-rapamycin (Compound A hereinafter), 40-[3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate]-rapamycin (also called CCI779), 40-epi-(tetrazolyl)-rapamycin (also called

ABT578), 32-deoxorapamycin, 16-pent-2-ynyloxy-32(S)-dihydro rapamycin, or TAFA-93. Even more preferred is Compound A.

Rapamycin derivatives also include so-called rapalogs, e.g. as disclosed in WO 98/02441 and WO 01/14387, e.g. AP23573, AP23464, or AP23841.

Rapamycin and derivatives thereof have, on the basis of observed activity, e.g. binding to macrophilin-12 (also known as FK-506 binding protein or FKBP-12), e.g. as described in WO 94/09010, WO 95/16691 or WO 96/41807, been found to be useful e.g. as immuno-suppressant, e.g. in the treatment of acute allograft rejection.

It has now been found that rapamycin and derivatives thereof are useful for the treatment of abnormally increased bone turnover or resorption.

In accordance with the particular findings of the present invention, there is provided:

1. A method for treating abnormally increased bone turnover or resorption in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of rapamycin or a rapamycin derivative.

In particular, there is provided:

1.1 A method for treating osteoporosis, e.g. postmenopausal osteoporosis, postmenopausal bone loss; male osteoporosis; corticosteroid-induced osteoporosis, in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of rapamycin or a rapamycin derivative.

1.2 A method for treating bone loss secondary to or due to medication, e.g. diphenylhydantoin, thyroid hormone replacement therapy; in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of rapamycin or a rapamycin derivative.

1.3 A method for treating bone loss associated with immobilisation and space flight; in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of rapamycin or a rapamycin derivative.

1.4 A method for treating bone loss associated with rheumatoid arthritis, osteopenia, osteogenesis imperfecta, hyperthyroidism, anorexia nervosa, organ transplantation, joint prosthesis loosening, in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of rapamycin or a rapamycin derivative.

1.5 A method for treating periarticular bone erosions in rheumatoid arthritis, in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of rapamycin or a rapamycin derivative.

1.6 A method for treating osteoarthritis, e.g. subchondral osteosclerosis, subchondral bone cysts, osteophyte formation, and of osteoarthritic pain, e.g. by reduction in intra-osseous pressure, in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of rapamycin or a rapamycin derivative.

1.7 A method for treating hypercalcemia, e.g. tumour-induced hypercalcemia, e.g. resulting from excessive bone resorption secondary to hyperparathyroidism, thyrotoxicosis, sarcoidosis or hypervitaminosis D, in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of rapamycin or a rapamycin derivative.

1.8 A method for treating bone cancer and bone metastases, in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of rapamycin or a rapamycin derivative; in particular a method for treating bone cancer and bone metastases induced by a primary tumour, e.g. breast or prostate cancer.

1.9 A method for treating multiple myeloma, in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of rapamycin or a rapamycin derivative.

In the present description the terms "treatment" or "treat" refer to both prophylactic or preventive treatment as well as curative or disease modifying treatment, including treatment of patients at risk of contracting the disease or suspected to have contracted the disease as well as patients who are ill or have been diagnosed as suffering from a disease or medical condition.

In a series of further specific or alternative embodiments, the present invention also provides:

2. Rapamycin or a rapamycin derivative for use in any method as defined under 1, in particular under 1.1 to 1.9 above.

3. Rapamycin or a rapamycin derivative for use in the preparation of a pharmaceutical composition for use in any method as defined under 1, in particular under 1.1 to 1.9 above.

4. A pharmaceutical composition for use in any method as defined under 1, in particular under 1.1 to 1.9 above, comprising rapamycin or a rapamycin derivative together with one or more pharmaceutically acceptable diluents or carriers therefore.

Rapamycin or a rapamycin derivative may be administered as the sole drug or in combination with a second drug. Suitable drugs for combination include a bone resorption inhibitor, e.g. as in osteoporosis therapy, in particular a calcitonin or an analogue or derivative thereof, e.g. salmon, eel or human calcitonin; a steroid hormone, e.g. an estrogen, a partial estrogen agonist or estrogen-gestagen combination; a selective estrogen receptor modulator (SERM) e.g. raloxifene, lasofoxifene, TSE-424, FC1271; tibolone (Livial ®); vitamin D or an analogue thereof; Parathyroid Hormone (PTH), a PTH fragment or a PTH derivative e.g. PTH (1-84), PTH (1-34), PTH (1-36), PTH (1-38), PTH (1-31)NH2 or PTS 893; a bisphosphonate e.g. alendronate, zoledronic acid, ibandronate; a cathepsin K inhibitor; PTH releaser; a selective androgen receptor molecule (SARM); metalloprotease (MMP) inhibitor; or strontium ranelate.

Accordingly, in another aspect, the present invention provides:

5. A pharmaceutical combination comprising a) rapamycin or a rapamycin derivative, and b) a second drug, e.g. as exemplified above.

6. A method as defined above comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective amount of rapamycin or a rapamycin derivative, and a second drug, e.g. as exemplified above.

The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the drugs are administered together, one after the other or separately in one combined unit dosage form or in two separate unit dosage forms but also in which the drugs are not necessarily administered by the same route of administration or at the same time. A unit dosage form may also be a fixed combination.

Utility of the compounds of the invention in treating diseases and conditions as hereinabove specified, may be demonstrated in standard animal or clinical tests, e.g. in accordance with the methods described hereinafter.

A. In vitro

A.1 Mouse Osteoclastogenesis Assay

Non-adherent bone marrow mononuclear cells from 5-week-old male mice cells are differentiated into bone-resorbing osteoclasts by treatment with a cytokine cocktail containing receptor activator of NF kappa B ligand (RANKL), macrophage-colony stimulating factor (M-CSF) and interleukin-1 (IL-1) alpha. Osteoclast formation is measured after 6 days by quantifying the number of tartrate-resistant acid phosphatase (TRAP)-positive multinucleated cells generated in plastic wells on a 48-well plate. Osteoclast activity is measured after 12 days by quantifying the area of resorbed dentine slices placed in wells on a 48-well plate. Treatment with rapamycin or the rapamycin derivative, e.g. Compound A, starts at the beginning of cell culture, together with the cytokine treatment.

Osteoblast differentiation is evaluated in mouse pre-osteoblastic cell line MC3T3-1b, stimulated to differentiate with osteogenic stimulus (a mixture of bone morphogenetic protein 2 (BMP-2), ascorbic acid and beta-glycerophosphate). Osteoplast activity is measured by quantifying culture area covered with alkaline phosphate-positive cells on a 48-well plate. Treatment with rapamycin or the rapamycin derivative, e.g. Compound A, starts at the beginning of cell culture, together with the osteogenic stimulus treatment.

In this assay, rapamycin or the rapamycin derivatives inhibit osteoclast formation and activity at an $IC_{50} < 1\mu m$.

Using Compound A, osteoclast formation is inhibited with an IC_{50} of 10.5 ± 4.6 nM and osteoclast activity with an IC_{50} of 0.6 ± 0.3 nM for osteoclast activity. Alkaline phosphatase (ALP) staining has an IC_{50} of 13.5 ± 2.4 nM.

A.2 Human Osteoclastogenesis Assay

Peripheral blood mononuclear cells from healthy male donors are differentiated into bone-resorbing osteoclasts by treatment with a cytokine cocktail containing RANKL, M-CSF and transforming growth factor (TGF)-beta 1. Osteoclast formation is measured after 17 days by quantifying the number of TRAP-positive multinucleated cells generated in plastic wells on a 96-well plate. Osteoclast activity is measured after 17 days by quantifying the area of resorbed bone on bovine cortical bone slices placed in wells on a 96-well plate. Treatment with rapamycin or the rapamycin derivative, e.g. Compound A, starts at the beginning of cell culture, together with the cytokine treatment. Collagen fragments are measured by enzyme linked immunosorbent assay (ELISA).

In this assay, rapamycin or the rapamycin derivatives inhibit osteoclast formation at an $IC_{50} < 1\mu m$.

Using Compound A, osteoclast formation is inhibited with an IC_{50} values of 7.7 ± 1.1 nM. Resorbed ares is inhibited with an IC_{50} of 3.4 ± 0.3 nM. Collagen fragment release is inhibited with an IC_{50} of 4.0 ± 0.5 nM.

Rapamycin and rapamycin derivatives are evaluated for in vivo bone resorption inhibition in an animal model e.g. as disclosed in Shinoda et al., Calcif. Tissue Int., 1983, 35, 87-99 or Schenk et al. Calcif. Tissue Res. 1973, 11, 196-214, or e.g. as disclosed hereinafter.

A.3 Gene expression is analyzed according to a method known in the art, in human osteoclasts after treatment with rapamycin or a derivative thereof. In particular, it is found that the expression of the osteoclast-specific protease cathepsin K is reduced, e.g. by about 78% for Compound A, and the expression of the Cdc2-related serine/threonine PFTAIRE1 is increased, e.g. by about 300% for Compound A.

B. In vivo: Ovariectomized rat model

Before operation, the tibial bone mass and geometry of the animals is measured at baseline by dual-energy x-ray absorptiometry (DEXA) and periphere quantitative computer tomography (pQCT). Following ovariectomy (OVX) or sham operation, skeletally mature rats are treated for 8 weeks daily with 0.15 mg/kg, 0.5 mg/kg, 1.5 mg/kg, or 3.0 mg/kg of rapamycin or a rapamycin derivative, e.g. Compound A, or vehicle alone by oral administration or once a week with 1.5 mg/kg or 5.0 mg/kg of rapamycin or a rapamycin derivative, e.g. Compound A. At the beginning of the treatment, animals receive a fluorochrome label, e.g. calcein (e.g. 30mg/kg, subcutaneous (s.c.)). Changes in bone mass and geometry (pQCT, DEXA) are evaluated in vivo after 4 weeks of treatment and at 8 weeks before necropsy. Body weight is monitored weekly. The animals are administered two further fluorochrome labels for marking of bone mineralization prior to necropsy, e.g. alizarin e.g. 20mg/kg, s.c., 10 days prior to necropsy, and calcein e.g. 30mg/kg, s.c., 3 days prior to necropsy. Blood samples (500µl blood) are taken in heparin before necropsy and frozen at -20°C for analysis of calcium, phosphate, TRAP, ALP, and osteocalcin. DEXA measurements are carried out at necropsy on excised tibia, femur, and lumbar vertebrae.

For example, Compound A reduces cancellous bone loss with 60% inhibition at 3 mg/kg/day, and inhibits reduction of trabecular number.

Daily dosages required in practicing the method of the present invention when rapamycin or a rapamycin derivative alone is used will vary depending upon, for example, the compound used, the host, the mode of administration and the severity of the condition to be treated. A preferred daily dosage range is about from 0.1 to 25 mg as a single dose or in divided doses. Suitable daily dosages for patients are on the order of from e.g. 0.1 to 25 mg p.o. Rapamycin or a rapamycin derivative may be administered by any conventional route, in particular enterally, e.g. orally, e.g. in the form of tablets, capsules, drink solutions, nasally, pulmonary (by inhalation) or parenterally, e.g. in the form of injectable solutions or suspensions. Suitable unit dosage forms for oral administration comprise from ca. 0.05 to 12.5 mg, usually 0.25 to 10 mg of rapamycin or a rapamycin derivative, e.g. Compound A, together with one or more pharmaceutically acceptable diluents or carriers therefor.

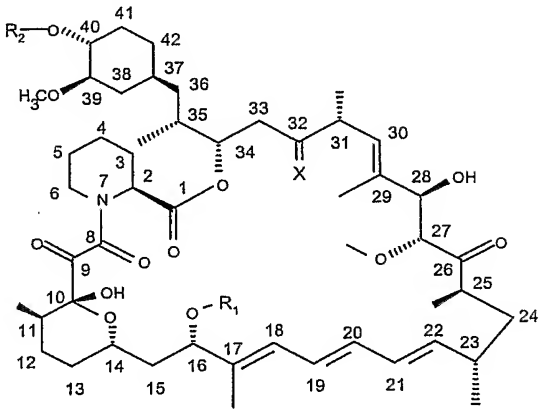
Due to synergism lower doses of the drugs of the combination of the invention may be used, for example, the dosages need not only often be smaller but are also applied less frequently, or may be used in order to diminish the incidence of side-effects. This is in accordance with the desires and requirements of the patients to be treated.

When rapamycin or the rapamycin derivative is co-administered with a second drug, dosages for the co-administered drug will of course vary depending on the type of drug employed, e.g. whether it is a steroid, a calcitonin or a biphosphonate, on the specific drug employed, on the condition to be treated, the severity of the condition being treated, whether it is a curative or preventive therapy, on the regimen and so forth.

The pharmaceutical compositions for separate administration of rapamycin or a rapamycin derivative and a second drug and for the administration in a fixed combination, i.e. a single galenical composition comprising at least two combination partners, according to the invention may be prepared in a manner known per se comprising a therapeutically effective amount of at least one pharmacologically active combination partner alone, e.g. as indicated above, or in combination with one or more pharmaceutically acceptable carriers or diluents.

CLAIMS

1. Use of a rapamycin derivative of formula I



I

wherein

R_1 is CH_3 or C_{3-6}alkynyl,

R_2 is H or $-CH_2-CH_2-OH$, 3-hydroxy-2-(hydroxymethyl)-2-methyl-propanoyl or tetrazolyl,

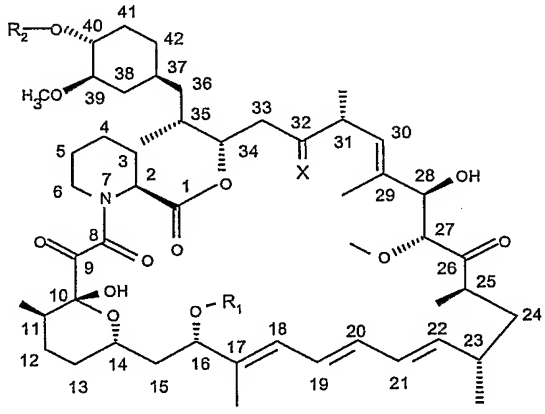
and X is =O, (H,H) or (H,OH),

provided that R_2 is other than H when X is =O and R_1 is CH_3,

or a prodrug thereof when R_2 is $-CH_2-CH_2-OH$, e.g. a physiologically hydrolysable ether thereof

in the preparation of a pharmaceutical composition for the treatment of abnormally increased bone turnover or resorption.

2. A pharmaceutical composition for use in the treatment of abnormally increased bone turnover or resorption comprising a rapamycin derivative of formula I



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wherein

R_1 is CH_3 or C_{3-6}alkynyl,

R_2 is H or $-CH_2-CH_2-OH$, 3-hydroxy-2-(hydroxymethyl)-2-methyl-propanoyl or tetrazolyl,

and X is =O, (H,H) or (H,OH),

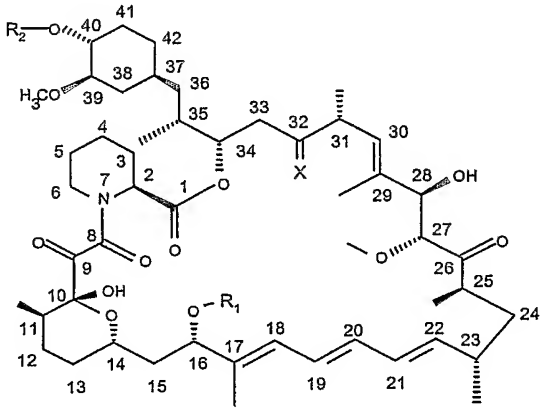
provided that R_2 is other than H when X is =O and R_1 is CH_3,

or a prodrug thereof when R_2 is $-CH_2-CH_2-OH$, e.g. a physiologically hydrolysable ether thereof,

together with one or more pharmaceutically acceptable diluents or carriers therefor.

3. A pharmaceutical combination comprising rapamycin or a rapamycin derivative and a second drug selected from bone resorption inhibitor, a calcitonin or an analogue or derivative thereof; a steroid hormone, a partial estrogen agonist or estrogen-gestagen combination; a selective estrogen receptor modulator; vitamin D or an analogue thereof; Parathyroid Hormone (PTH), a PTH fragment or a PTH derivative; a bisphosphonate; a cathepsin K inhibitor; a PTH releaser; a selective androgen receptor molecule; and strontium ranelate.

4. A method for treating abnormally increased bone turnover or resorption in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a rapamycin derivative of formula I



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wherein

R_1 is CH_3 or C_{3-6}alkynyl,

R_2 is H or $-CH_2-CH_2-OH$, 3-hydroxy-2-(hydroxymethyl)-2-methyl-propanoyl or tetrazolyl,

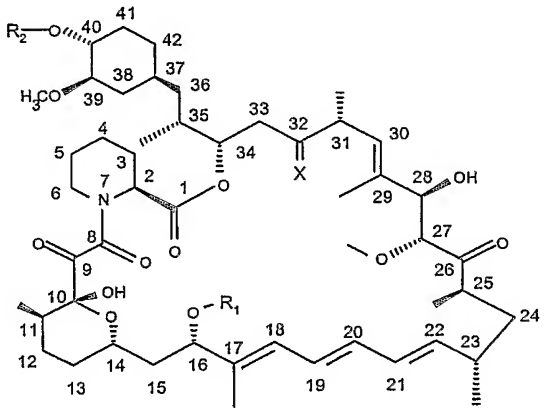
and X is =O, (H,H) or (H,OH),

provided that R_2 is other than H when X is =O and R_1 is CH_3,

or a prodrug thereof when R_2 is $-CH_2-CH_2-OH$, e.g. a physiologically hydrolysable ether thereof.

5. A method for treating abnormally increased bone turnover or resorption in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of rapamycin or a rapamycin derivative, concomitantly or sequentially with a second drug selected from bone resorption inhibitor, a calcitonin or an analogue or derivative thereof; a steroid hormone, a partial estrogen agonist or estrogen-gestagen combination; a selective estrogen receptor modulator; vitamin D or an analogue thereof; Parathyroid Hormone (PTH), a PTH fragment or a PTH derivative; a bisphosphonate; a cathepsin K inhibitor; a PTH releaser; a selective androgen receptor molecule; and strontium ranelate.

6. Combination of claim 3 or method according to claim 5 wherein the rapamycin derivative is a compound of formula I



I

wherein

R_1 is CH_3 or C_{3-6}alkynyl,

R_2 is H or $-CH_2-CH_2-OH$, 3-hydroxy-2-(hydroxymethyl)-2-methyl-propanoyl or tetrazolyl, and X is =O, (H,H) or (H,OH),

provided that R_2 is other than H when X is =O and R_1 is CH_3,

or a prodrug thereof when R_2 is $-CH_2-CH_2-OH$, e.g. a physiologically hydrolysable ether thereof.

7. Use, composition, combination or method according to any preceding claim wherein the rapamycin derivative is selected from 40-O-(2-hydroxyethyl)-rapamycin, 40-[3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate]-rapamycin, 40-epi-(tetrazolyl)-rapamycin, 32-deoxorapamycin, 16-pent-2-ynyloxy-32(S)-dihydro rapamycin, and TAFA-93.

8. Use, composition, combination or method according to any preceding claim wherein the rapamycin derivative is 40-O-(2-hydroxyethyl)-rapamycin.

9. Use, composition, combination or method according to any preceding claim for the treatment of osteoporosis; bone loss secondary to or due to medication; bone loss associated with immobilisation and space flight; bone loss associated with rheumatoid arthritis, osteopenia, osteogenesis imperfecta, hyperthyroidism, anorexia nervosa, organ transplantation, joint prosthesis loosening; periarticular bone erosions in rheumatoid arthritis; osteoarthritis; hypercalcemia; bone cancer and bone metastases; and/or multiple myeloma.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/007437

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D498/18 A61K31/436 A61P19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, WPI Data, PAJ, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 258 389 A (GOULET MARK ET AL) 2 November 1993 (1993-11-02) claim 1 column 24, line 31 - line 32	1,2,4, 6-8
X	US 5 527 907 A (OR YAT S ET AL) 18 June 1996 (1996-06-18) claim 1 column 90, line 13	1,2,4, 6-8

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 October 2004	22/10/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Beranová, P

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/007437

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHUI C ET AL: "The immunosuppressant rapamycin, alone or with transforming growth factor-beta, enhances osteoclast differentiation of RAW264.7 monocyte-macrophage cells in the presence of RANK-ligand." CALCIFIED TISSUE INTERNATIONAL, vol. 71, no. 5, November 2002 (2002-11), pages 437-446, XP002299513 ISSN: 0171-967X	1,2,4, 6-8
Y	page 444, left-hand column, last paragraph	1,2,4, 6-8
Y	ROMERO DAVID F ET AL: "Rapamycin: A bone sparing immunosuppressant?" JOURNAL OF BONE AND MINERAL RESEARCH, vol. 10, no. 5, 1995, pages 760-768, XP008036532 ISSN: 0884-0431 page 766, right-hand column	1,2,4, 6-8
X	VAN ETTEN EVELYNE ET AL: "Analogs of 1,25-dihydroxyvitamin D3 as dose-reducing agents for classical immunosuppressants" TRANSPLANTATION (BALTIMORE), vol. 69, no. 9, 15 May 2000 (2000-05-15), pages 1932-1942, XP008036525 ISSN: 0041-1337 page 1932, left-hand column	3,6,7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/007437

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 4 and 5 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

[redacted]national Application No
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